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(54) AGENT FOR SUPPRESSING GENERATION OF ACTIVE OXYGEN AND AGENT FOR PREVENTING DISEASE CAUSED BY ACTIVE OXYGEN

(57)Abstract:

PROBLEM TO BE SOLVED: To provide an agent effective for suppressing the generation of active oxygen and preventing the diseases caused by active oxygen based on the new concept that an extracted tea component acts on the generation system of active oxygen and suppresses the generation of active oxygen from its origin.

SOLUTION: This agent for suppressing the generation of active oxygen and preventing diseases caused by active oxygen is produced by using a warm water or hot water extract of tea as an active component. The extract is especially tea catechin, i.e., catechins extracted from tea, above all one or more compounds selected from epicatechin, epigallocatechin, epicatechin gallate and epigallocatechin gallate. Active oxygen is e.g. superoxide anion (O2-), hydroxy radical (.OH), hydrogen peroxide, etc., generated in the body and the diseases caused by active oxygen are periodontosis, pneumonia, aging, cancer, etc., caused by active oxygen.

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CLAIMS

[Claim(s)]
[Claim 1] The active oxygen generating inhibitor which carries out the active principle of brown warm water or a brown hot water extract, and contains it.
[Claim 2] The active oxygen generating inhibitor which carries out the active principle of the tea catechin, and contains it.
[Claim 3] Epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, or the active oxygen generating inhibitor that contains these two or more kinds as an active principle.
[Claim 4] The active oxygen reason disease prevention agent which carries out the active principle of brown warm water or a brown hot water extract, and contains it.
[Claim 5] The active oxygen reason disease prevention agent which contains a tea catechin as an active principle.
[Claim 6] Epicatechin, epigallocatechin, epicatechin gallate, epigallocatechin gallate, or the active oxygen reason disease prevention agent that contains these two or more kinds as an active principle.

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DETAILED DESCRIPTION

[Detailed Description of the Invention]
[0001]
[Field of the Invention] This invention controls generating of the active oxygen in the inside of the body, and relates to the drugs which can prevent various diseases which originate in active oxygen, such as inflammation, aging, oncogenesis, and myocardial infarction, and are produced.
[0002]
[Description of the Prior Art] Active oxygen, such as a superoxide anion (O2-), a HIDOROSHIKI radical (-OH), and a hydrogen peroxide, is said to cause various diseases, such as a lifting, inflammation, aging, oncogenesis, and myocardial infarction, for an organization trauma, if it generates so much in the living body. Especially the hydroxy radical is considered for activity to be high, and to attack to a living body in diffusion limitation, to draw out H from lipids, such as a cell membrane, and to cause inflammation and various diseases by making a lipid into a peroxylipid radical also in active oxygen.
[0003] On the other hand, the living body has some enzymes for reducing various active oxygen. For example, although super-oxide dismutase (SOD) changes a superoxide anion into a hydrogen peroxide by disproportionation, it is supposed that a catalase and glutathione peroxidase eliminate a hydrogen peroxide. However, the enzyme which reduces these about a part of [, such as a hydroxy radical,] active oxygen is not discovered in the living body, and may fully be unable to reduce active oxygen only with a living body's enzyme in respect of effect. Then, in order to prevent various diseases resulting from active oxygen, it is necessary to supply the matter which disappears active oxygen, or the matter which controls generating of active oxygen fundamentally to a living body.
[0004] Conventionally, in JP,59-166585,A, a tea extract component is not indicated about reduction of active oxygen, although invention of the anti-oxidant of the food grade which carried out the active principle of tannin matter drawing especially epicatechin, epigallocatechin, epicatechin gallate, and the epigallocatechin gallate, and cosmetics is indicated. Moreover, although invention of the active oxygen free radical elimination agent which makes an active principle the condensation mold tannin separated from tea was indicated by JP,64-25726,A, it says that the active oxygen generated in the body eliminates this invention so that "elimination" may mean, and it acted on the generating system of active oxygen, and the technical thought of controlling the generating itself was not indicated.
[0005] As a result of inquiring wholeheartedly that the mechanism to which a tea extract component acts on the generating system of active oxygen should be studied, this invention persons can do new discovery which can be referred to as reversing the conventional view, and make this time based on this discovery.
[0006]
[Means for Solving the Problem] That is, as a result of wholeheartedly research of this invention persons, it discovers that a tea extract component acts on the generating system of active oxygen rather than eliminates the active oxygen generated in the body, and controls the generating of active oxygen itself, and the following this inventions are reached based on this discovery.

[0007] The first of this invention, it is the active oxygen generating inhibitor which contains the catechins extracted from brown warm water or a hot water extract, especially a tea catechin, i.e., tea, as an active principle. The active oxygen in this invention means the active oxygen (O2-), i.e., a superoxide anion, generated in a body, the HIDOROSHIKI radical (-OH), the hydrogen peroxide, etc.
[0008] It is the active oxygen reason disease prevention agent which contains the catechins extracted from the warm water of the second tea or hot water extract, especially tea catechin of this invention, i.e., tea, as an active principle. The active oxygen reason disease in this invention means diseases, such as the Alzheimer mold Alzheimer's disease by the toxicity of beta amyloid protein, in cardiovascular disease, such as myocardial infarction resulting from the lung cancer resulting from gum disease, such as the disease resulting from active oxygen, i.e., gingivitis, and periodontitis, pneumonia, aging, an initiator, or a promotor and gastric cancer, and arteriosclerosis, and a list.
[0009] The tea in above-mentioned this invention is tea originating in Theaceae, and a tea catechin means the catechins, i.e., epicatechin gallate, contained to these tea, epigallocatechin gallate, epicatechin, epigallocatechin, or these two kinds or more. Epicatechin gallate or epigallocatechin gallate is especially considered to be a desirable thing.
[0010] As brown warm water or a brown hot water extract, hot water extract processing of the green tea is carried out, for example. The green tea extractives (Ito En trade name: TEAFURAN 30) which were made to dry this extract and made catechin concentration about 22%, Carry out hot water extract processing of the green tea, and in order to eliminate components other than a catechin, process this extract with a column method and it is dried. The green tea extractives (Ito En trade name: TEAFURAN 90S) which made catechin concentration about 85% are suitable examples at the point of fully containing a tea catechin and being easy to receive.
[0011] Moreover, in above-mentioned this invention, even when warm water or a brown hot water extract thru/or a brown tea catechin is independent, it is effective as an active oxygen generating inhibitor or an active oxygen reason disease prevention agent, but if vitamin A (carotinoids), vitamin C, vitamin E, a glutathione, an organic acid, amino acid, etc. are blended, it can heighten effectiveness further. When using especially as drugs or quasi drugs, it is desirable to blend vitamin A (carotinoids), vitamin C, vitamin E, and a glutathione.
[0012] Moreover, making it dry by freeze drying or spray drying, and providing as desiccation powder can also offer the pharmaceutical form of the active oxygen generating inhibitor of this invention, or an active oxygen reason disease prevention agent as liquids and solutions, a tablet, powder, granulation, sugar-coated tablet, a capsule, suspension, liquids and solutions, an emulsion, ampul, injections, etc.
[0013] Moreover, the active oxygen generating inhibitor of this invention and an active oxygen reason disease prevention agent can be variously offered as drugs, quasi drugs (cosmetics, mouth wash, etc. are included), health food, a health drink, etc. For example, it prepares as quasi drugs, and if this is made easy to take in daily as a gestalt of drink gestalten, such as a can drink drink and a bottle drink drink, or a tablet, a capsule, granulation, etc., it can provide by taking in daily as quasi drugs which bring about sufficient pharmacology effectiveness to a living body.
[0014]
[Embodiment of the Invention]
(Cu2+/H2O2 Measurement of the reduction ability of the hydroxy radical generated from the system of reaction) This example DMSO (dimethyl sulfoxide) known as tea extractives (Ito En TEAFURAN 30, Ito En TEAFURAN 90 S) and a hydroxy radical elimination agent ******** -- Cu2+/H2O2 Hydroxy radical reduction ability generated from the system of reaction is measured. DMPO which is especially a spin-trapping agent (5 and 5-Dimethyl-1-pyrroline-N-oxide) By changing concentration and changing a rate of reaction, hydroxy radical reduction ability is examined from a kinetics-standpoint.
[0015] (Adjustment of a sample) TEAFURAN 30 is the green tea extractives which hot water extract processing of the green tea is carried out, it is the green tea extractives which dried this extract, and TEAFURAN 90S carry out hot water extract processing of the green tea, and this extract was processed [extractives] with the column method and dried it in order to eliminate components other than catechins. Both catechin content (% of the weight) is shown below.

[0016]
TEAFURAN 30 TEAFURAN 90S epigallocatechin (EGC) ..... 12.30 2.00 epigallocatechin gallate (EGCg) .. 6.84 66.26 epicatechin (EC) ..... 1.64 below limit-of-detection epicatechin gallate (ECg) ..... 1.05 15.29 [0017] moreover, DMSO (dimethyl sulfoxide) the thing by the Wako Pure Chem industrial company -- using it -- DMPO (5 and 5-Dimethyl-1-pyrroline-N-oxide) said -- Renhua -- what was purchased from the study lab company was used. The above sample was prepared to various concentration with pure water.
[0018] (Measuring method) DMPO20microl [of CuCl2 50microl of last concentration 1mM, pure-water 30microl, 9.2mM, or 92mM(s)] and 100 H2O250microl of mM and 50micro of each sample 1 were mixed and (total amount 200microl) stirred in this sequence, and it drew in in the particular flat cel. From this, it is Cu2+/H2O2. If each sample is made to react to the hydroxy radical generated from the system of reaction and a trap is carried out by DMPO of a spin-trapping agent, it can consider as DMPO-OH adduct. Measurement was measured after [of reaction initiation] 50 seconds using ESR equipment (radical biosensor FR 80 by JEOL Co., Ltd.).
[0019] Drawing 1 is the graph which showed relation with TEAFURAN 30, TEAFURAN 90S, and the concentration of DMSO and DMPO-OH yield at the time of setting DMPO concentration to 9.2mM(s). Drawing 2 It is the graph which showed the relation between TEAFURAN 30 concentration at the time of setting DMPO concentration to 92mM(s) or 9.2mM(s), and DMPO-OH yield. Drawing 3 It is the graph which showed the relation between TEAFURAN 90S concentration at the time of setting DMPO concentration to 92mM(s) or 9.2mM(s), and DMPO-OH yield.
[0020] (A result and consideration) Each of TEAFURAN 30 from the result of drawing 1 and TEAFURAN 90S is Cu2+/H2 O2. Reducing the hydroxy radical (-OH) generated from the system of reaction was confirmed, and the direction of TEAFURAN 90S of the reduction capacity was size from TEAFURAN 30. On the other hand, even if it changed the concentration of DMPO which is the trap agent of ESR spin trapping and changed the reaction rate from the result of drawing 2 and drawing 3 , it was changeless to a sigmoid curve. TEAFURAN 30 this [whose] is green tea extractives, and TEAFURAN 90S will not have eliminated the hydroxy radical (-OH) directly, would act on the 2OCu2+/H2 system of reaction, and will have controlled the generating of a hydroxy radical (-OH) itself as a result. Therefore, it is thought that each of TEAFURAN 30 and TEAFURAN 90S (green tea extract) is effective also as preventive of various diseases resulting from active oxygen generating because they controls generating of a hydroxy radical while they is effective as a hydroxy radical generating inhibitor, i.e., an active oxygen generating inhibitor.
[0021] In addition, although the Cu2+ signal was shifted when a Cu2+ signal was measured by ESR in the above-mentioned measurement, and EDTA was added, even if it added TEAFURAN 90S, the Cu2+ signal was not shifted, but it was checked TEAFURAN 30 and that the amount of signals had decreased. TEAFURAN 30 this [whose] is green tea extractives, and TEAFURAN 90S change Cu2+ by carrying out coordinate bond to self rather than carrying out chelate formation of Cu2+ like EDTA, or carrying out a certain chemical bond, and are considered to have decreased the amount of Cu2+.
[0022] Next, in TEAFURAN 30, ID50 of 7.98mM(s) and DMPO concentration 9.2mM of ID50 of DMPO concentration 92mM was 6.86mM(s) from the result of drawing 2 , and the averages of ID50 were 7.42mM(s). In the case of TEAFURAN 90S, from the result of drawing 3 , ID50 of 0.44mM(s) and DMPO concentration 9.2mM of ID50 of DMPO concentration 92mM was 0.52mM(s), and the averages of ID50 were 0.48mM(s).
[0023] When TEAFURAN 30 and average ID50 value of TEAFURAN 90S were compared from the above result, ID50 of TEAFURAN 30 was 15.46 times compared with ID50 of TEAFURAN 90S. The direction of TEAFURAN 90S compares with TEAFURAN 30, and this result is Cu2+/H2O2. [that it is shown that the rate of control of the hydroxy radical (-OH) in the system of reaction is high, and] If TEAFURAN 30 and the component ratio of TEAFURAN 90S are made to correlate and it thinks The point which is about 15 times whose epicatechin gallate (ECg) concentration of TEAFURAN 30 is TEAFURAN 90S to Cu2+/H2O2 It is thought that possibility that ECg is participating in the generating system of the hydroxy radical in the system of reaction is high. However, the sigmoid curve of drawing

2 and drawing 3 will lengthen, and ID50 of TEAFURAN 30 will serve as about 5 mM extent depending on the direction, consequently ID50 of TEAFURAN 30 will be about 10 times ID50 of TEAFURAN 90S. The point which is about 10 times whose epigallocatechin gallate (EGCg) concentration of TEAFURAN 30 is TEAFURAN 90S when this result is made to correlate with TEAFURAN 30 and the component ratio of TEAFURAN 90S and is considered to Cu2+/H2O2 It is thought that EGCg may be participating in the generating system of the hydroxy radical in the system of reaction.
[0024] (Example 1) The mouth wash contained under the category of cosmetics with active oxygen generating depressor effect and the active oxygen generating reason disease prevention effectiveness or quasi drugs was created by the following blending ratio of coal so that TEAFURAN 30 might be set to 6 or more mMs and TEAFURAN 90S might be set the concentration of 0.6 or more mMs. In addition, 6mM(s) of above-mentioned TEAFURAN 30 and the numeric value of 0.6mM(s) of TEAFURAN 90S are values based on the concentration corresponding to ID50 at the time of drawing a sigmoid curve, respectively in drawing 1 .
green tea extractives ..... 1.0 Weight % paraoxybenzoic acid - 0.05-% of the weight propylene glycol .... 1.0 weight % concentrated glycerin ..... 1.0 a weight % sodium citrate ..... 0.05-% of the weight perfume ..... optimum dose purified water ..... 95.0 Weight % [0025] (Example 2) Green tea extractives (TEAFURAN 30 or TEAFURAN 90S) were blended at following rate, and food with the effectiveness which prevents aging of lipid peroxidation etc., or drugs was created by controlling generating of a hydroxy radical.
A tea catechin ..... 70.0mg Vitamin C ..... 50.0mg An emulsification oligosaccharide ..... 90.0mg A granulation agent ..... 60.0mg Crystalline cellulose ..... 80.0mg a reduction maltose starch syrup ..... 90.0mg shoe cloth ..... 60.0mg perfume ..... Optimum dose (sum total) .. 500.0mg

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TECHNICAL FIELD

[Field of the Invention] This invention controls generating of the active oxygen in the inside of the body, and relates to the drugs which can prevent various diseases which originate in active oxygen, such as inflammation, aging, oncogenesis, and myocardial infarction, and are produced.

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TECHNICAL PROBLEM

[Description of the Prior Art] Active oxygen, such as a superoxide anion (O2-), a HIDOROSHIKI radical (-OH), and a hydrogen peroxide, is said to cause various diseases, such as a lifting, inflammation, aging, oncogenesis, and myocardial infarction, for an organization trauma, if it generates so much in the living body. Especially the hydroxy radical is considered for activity to be high, and to attack to a living body in diffusion limitation, to draw out H from lipids, such as a cell membrane, and to cause inflammation and various diseases by making a lipid into a peroxylipid radical also in active oxygen.

[0003] On the other hand, the living body has some enzymes for reducing various active oxygen. For example, although super-oxide dismutase (SOD) changes a superoxide anion into a hydrogen peroxide by disproportionation, it is supposed that a catalase and glutathione peroxidase eliminate a hydrogen peroxide. However, the enzyme which reduces these about a part of [, such as a hydroxy radical,] active oxygen is not discovered in the living body, and may fully be unable to reduce active oxygen only with a living body's enzyme in respect of effect. Then, in order to prevent various diseases resulting from active oxygen, it is necessary to supply the matter which disappears active oxygen, or the matter which controls generating of active oxygen fundamentally to a living body.

[0004] Conventionally, in JP,59-166585,A, a tea extract component is not indicated about reduction of active oxygen, although invention of the anti-oxidant of the food grade which carried out the active principle of tannin matter drawing especially epicatechin, epigallocatechin, epicatechin gallate, and the epigallocatechin gallate, and cosmetics is indicated. Moreover, although invention of the active oxygen free radical elimination agent which makes an active principle the condensation mold tannin separated from tea was indicated by JP,64-25726,A, it says that the active oxygen generated in the body eliminates this invention so that "elimination" may mean, and it acted on the generating system of active oxygen, and the technical thought of controlling the generating itself was not indicated.

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MEANS

[Means for Solving the Problem] That is, as a result of wholeheartedly research of this invention persons, it discovers that a tea extract component acts on the generating system of active oxygen rather than eliminates the active oxygen generated in the body, and controls the generating of active oxygen itself, and the following this inventions are reached based on this discovery.
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[0011] Moreover, in above-mentioned this invention, even when warm water or a brown hot water extract thru/or a brown tea catechin is independent, it is effective as an active oxygen generating inhibitor or an active oxygen reason disease prevention agent, but if vitamin A (carotinoids), vitamin C, vitamin E, a glutathione, an organic acid, amino acid, etc. are blended, it can heighten effectiveness further. When using especially as drugs or quasi drugs, it is desirable to blend vitamin A (carotinoids), vitamin C, vitamin E, and a glutathione.
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[0018] (Measuring method) DMPO20microl [of CuCl2 50microl of last concentration 1mM, pure-water 30microl, 9.2mM, or 92mM(s)] and 100 H2O250microl of mM and 50micro of each sample 1 were mixed and (total amount 200microl) stirred in this sequence, and it drew in in the particular flat cel. From this, it is Cu2+/H2O2. If each sample is made to react to the hydroxy radical generated from the system of reaction and a trap is carried out by DMPO of a spin-trapping agent, it can consider as DMPO-OH adduct. Measurement was measured after [of reaction initiation] 50 seconds using ESR equipment (radical biosensor FR 30 by JEOL Co., Ltd.).
[0019] Drawing 1 is the graph which showed relation with TEAFURAN 30, TEAFURAN 90S, and the concentration of DMSO and DMPO-OH yield at the time of setting DMPO concentration to 9.2mM(s). Drawing 2 It is the graph which showed the relation between TEAFURAN 30 concentration at the time of setting DMPO concentration to 92mM(s) or 9.2mM(s), and DMPO-OH yield. Drawing 3 It is the graph which showed the relation between TEAFURAN 90S concentration at the time of setting DMPO concentration to 92mM(s) or 9.2mM(s), and DMPO-OH yield.
[0020] (A result and consideration) Each of TEAFURAN 30 from the result of drawing 1 and TEAFURAN 90S is Cu2+/H2 O2. Reducing the hydroxy radical (-OH) generated from the system of reaction was confirmed, and the direction of TEAFURAN 90S of the reduction capacity was size from TEAFURAN 30. On the other hand, even if it changed the concentration of DMPO which is the trap agent of ESR spin trapping and changed the reaction rate from the result of drawing 2 and drawing 3 , it was changeless to a sigmoid curve. TEAFURAN 30 this [whose] is green tea extractives, and TEAFURAN 90S will not have eliminated the hydroxy radical (-OH) directly, would act on the 2OCu2+/H2 system of reaction, and will have controlled the generating of a hydroxy radical (-OH) itself as a result. Therefore, it is thought that each of TEAFURAN 30 and TEAFURAN 90S (green tea extract) is effective also as preventive of various diseases resulting from active oxygen generating because they controls generating of a hydroxy radical while they is effective as a hydroxy radical generating inhibitor, i.e., an active oxygen generating inhibitor.
[0021] In addition, although the Cu2+ signal was shifted when a Cu2+ signal was measured by ESR in the above-mentioned measurement, and EDTA was added, even if it added TEAFURAN 90S, the Cu2+

signal was not shifted, but it was checked TEAFURAN 30 and that the amount of signals had decreased. TEAFURAN 30 this [whose] is green tea extractives, and TEAFURAN 90S change Cu2+ by carrying out coordinate bond to self rather than carrying out chelate formation of Cu2+ like EDTA, or carrying out a certain chemical bond, and are considered to have decreased the amount of Cu2+.

[0022] Next, in TEAFURAN 30, ID50 of 7.98mM(s) and DMPO concentration 9.2mM of ID50 of DMPO concentration 92mM was 6.86mM(s) from the result of drawing 2 , and the averages of ID50 were 7.42mM(s). In the case of TEAFURAN 90S, from the result of drawing 3 , ID50 of 0.44mM(s) and DMPO concentration 9.2mM of ID50 of DMPO concentration 92mM was 0.52mM(s), and the averages of ID50 were 0.48mM(s).

[0023] When TEAFURAN 30 and average ID50 value of TEAFURAN 90S were compared from the above result, ID50 of TEAFURAN 30 was 15.46 times compared with ID50 of TEAFURAN 90S. The direction of TEAFURAN 90S compares with TEAFURAN 30, and this result is Cu2+/H2O2. [that it is shown that the rate of control of the hydroxy radical (-OH) in the system of reaction is high, and] If TEAFURAN 30 and the component ratio of TEAFURAN 90S are made to correlate and it thinks The point which is about 15 times whose epicatechin gallate (ECg) concentration of TEAFURAN 30 is TEAFURAN 90S to Cu2+/H2O2 It is thought that possibility that ECg is participating in the gene g system of the hydroxy radical in the system of reaction is high. However, the sigmoid curve of dra g 2 and drawing 3 will lengthen, and ID50 of TEAFURAN 30 will serve as about 5 mM extent depe g on the direction, consequently ID50 of TEAFURAN 30 will be about 10 times ID50 of TEAFURAN 90S. The point which is about 10 times whose epigallocatechin gallate (EGCg) concentration of TEAFURAN 30 is TEAFURAN 90S when this result is made to correlate with TEAFURAN 30 a component ratio of TEAFURAN 90S and is considered to Cu2+/H2O2 It is thought that EGCg m participating in the generating system of the hydroxy radical in the system of reaction.

[0024] (Example 1) The mouth wash contained under the category of cosmetics with active oxyge generating depressor effect and the active oxygen generating reason disease prevention effectiven quasi drugs was created by the following blending ratio of coal so that TEAFURAN 30 might be or more mMs and TEAFURAN 90S might be set the concentration of 0.6 or more mMs. In additi 6mM(s) of above-mentioned TEAFURAN 30 and the numeric value of 0.6mM(s) of TEAFURAN are values based on the concentration corresponding to ID50 at the time of drawing a sigmoid cur respectively in drawing 1 .

green tea extractives ..... 1.0 Weight % paraoxybenzoic acid - 0.05-% of the weight propylene glycol .... 1.0 weight % concentrated glycerin ..... 1.0 a weight % sodium citrate .... 0.05-% of th weight perfume ..... optimum dose purified water ..... 95.0 Weight % [002] (Example 2) g tea extractives (TEAFURAN 30 or TEAFURAN 90S) were blended at following rate, and food w effectiveness which prevents aging of lipid peroxidation etc., or drugs was created by controlling generating of a hydroxy radical.

A tea catechin ..... 70.0mg Vitamin C ..... 50.0mg An emulsification oligosaccharide ..... 90.0mg A granulation agent ..... 60.0mg Crystalline cellulose ..... 80.0mg a reduction maltose starch syrup ..... 90.0mg shoe cloth ..... 60.0mg perfume ..... Optimum dose (sum total) .. 500.0mg

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DESCRIPTION OF DRAWINGS

[Brief Description of the Drawings]
[Drawing 1] It is the graph which showed the relation of the concentration of TEAFURAN 30, TEAFURAN 90S, and DMSO and DMPO-OH yield at the time of setting DMPO concentration to 9.2mM(s).
[Drawing 2] It is the graph which showed the relation between TEAFURAN 30 concentration at the time of setting DMPO concentration to 92mM(s) or 9.2mM(s), and DMPO-OH yield.
[Drawing 3] It is the graph which showed the relation between TEAFURAN 90S concentration at the time of setting DMPO concentration to 92mM(s) or 9.2mM(s), and DMPO-OH yield.

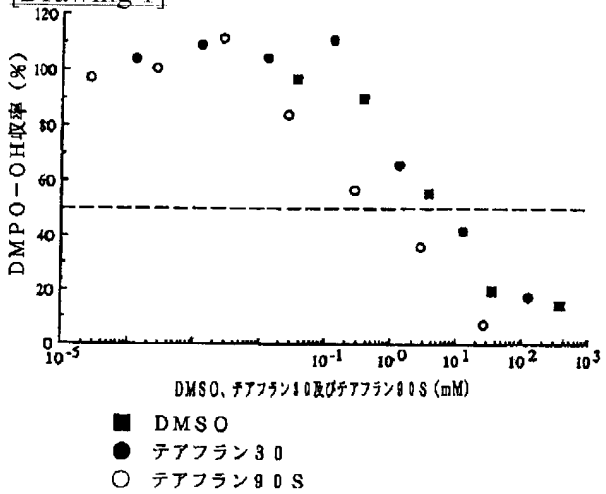
[Translation done.]

* NOTICES *

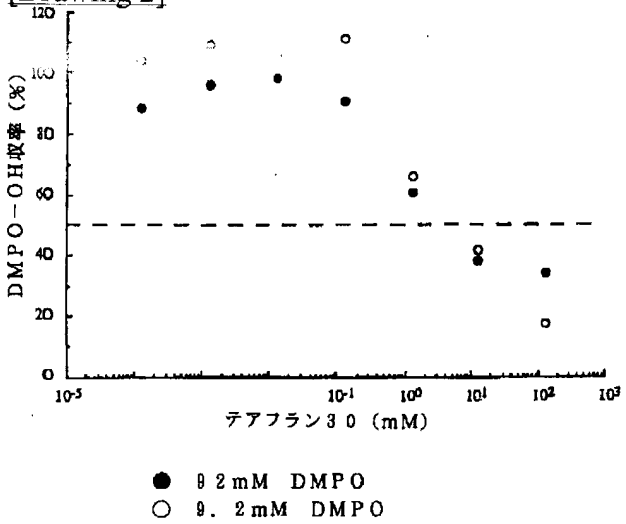
1.This document has been translated by computer. So the translation may not reflect the original precisely.
2.**** shows the word which can not be translated.
3.In the drawings, any words are not translated.

DRAWINGS

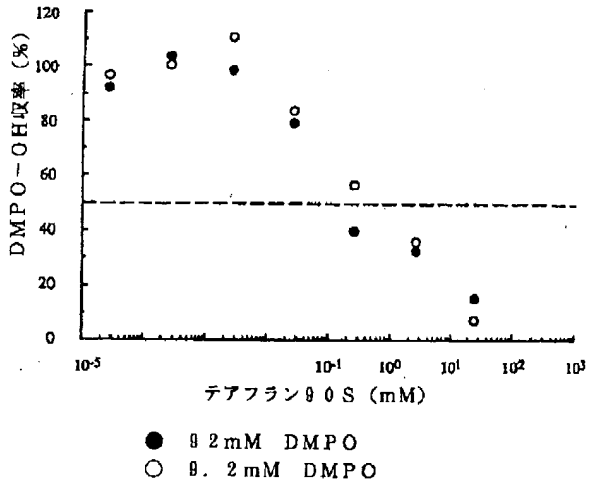
[Drawing 1]



[Drawing 2]



[Drawing 3]



[Translation done.]

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L7: Entry 43 of 43 File: DWPI Jun 30, 1998

DERWENT-ACC-NO: 1998-422298
DERWENT-WEEK: 199836

TITLE: Inhibition of super-oxide production or preventing super-oxide-derived disease - using warm/hot aqueous tea, used to prevent e.g. inflammation, ageing, carcinogenes, myocardial infarction, gingivitis and periodontitis

PATENT-ASSIGNEE: ITOEN KK (ITOEN)

PRIORITY-DATA: 1996JP-0334072 (December 13, 1996)

Search Selected Search ALL Clear

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 10175858 A	June 30, 1998		005	A61K031/35

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP 10175858A	December 13, 1996	1996JP-0334072	

INT-CL (IPC): A61 K 31/35; A61 K 35/78; C07 D 311/62

ABSTRACTED-PUB-NO: JP 10175858A
BASIC-ABSTRACT:

Inhibition of superoxide production or preventing superoxide-derived disease using warm/hot aqueous tea extract, is new. Also claimed are: (A) inhibition of superoxide production or preventing superoxide-derived disease using tea catechin; and (B) inhibition of superoxide production or preventing superoxide-derived disease using epicatechin, epigallocatechin, epicatechin gallate and/or epigallocatechin gallate.

USE - The superoxide inhibitors can be used to prevent disease caused by superoxide e.g. inflammation, ageing, carcinogenesis, myocardial infarction, gingivitis, periodontitis, pneumonia, senescence, cardiovascular disease, lung cancer or stomach cancer, Alzheimer type dementia due to toxicity of beta -amyloid protein.

ADVANTAGE - The aqueous extract of tea, tea catechin, epicatechin (EC), epigallocatechin (EGC), epicatechin gallate (ECg) or epigallocatechin gallate (EGCg) do not eliminate production of superoxide but inhibit over production.

ABSTRACTED-PUB-NO: JP 10175858A
EQUIVALENT-ABSTRACTS:

CHOSEN-DRAWING: Dwg.1/3

DERWENT-CLASS: B04
CPI-CODES: B05-A01B; B06-A01; B14-C03; B14-D05; B14-F01B; B14-F07; B14-H01; B14-N06B;

Previous Doc Next Doc Go to Doc#

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	ＡＢＳ		ＡＢＳ
	ＡＤＵ		ＡＤＵ
	ＡＥＤ		ＡＥＤＣ

審査請求　未請求　請求項の数６　ＯＬ　（全５頁）　最終頁に続く

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最終頁に続く

(54)【発明の名称】　活性酸素発生抑制剤及び活性酸素起因疾患予防剤

(57)【要約】

【課題】　茶抽出成分が、活性酸素の発生系に作用し活性酸素の発生そのものを抑制するという新たな考え方に基づき、活性酸素発生抑制効果及び活性酸素起因疾患予防剤を提供する。

【解決手段】　茶の温水又は熱水抽出物、特に茶カテキンすなわち茶から抽出されるカテキン類、中でもエピカテキン、エピガロカテキン、エピカテキンガレート、エピガロカテキンガレートのいずれか、或いはこれらの２種類以上を有効成分として活性酸素発生抑制剤及び活性酸素起因疾患予防剤を作成した。活性酸素とは、体内で発生するスーパーオキサイドアニオン（O_2^-）、ヒドロシキラジカル（・ＯＨ）、過酸化水素などであり、又、活性酸素起因疾患とは、活性酸素に起因する歯周病や肺炎、老化、癌などの疾患である。

1

【特許請求の範囲】

【請求項１】　茶の温水又は熱水抽出物を有効成分して含有する活性酸素発生抑制剤。

【請求項２】　茶カテキンを有効成分して含有する活性酸素発生抑制剤。

【請求項３】　エピカテキン、エピガロカテキン、エピカテキンガレート、エピガロカテキンガレートのいずれか、或いはこれらの２種類以上を有効成分として含有する活性酸素発生抑制剤。

【請求項４】　茶の温水又は熱水抽出物を有効成分して含有する活性酸素起因疾患予防剤。

【請求項５】　茶カテキンを有効成分として含有する活性酸素起因疾患予防剤。

【請求項６】　エピカテキン、エピガロカテキン、エピカテキンガレート、エピガロカテキンガレートのいずれか、或いはこれらの２種類以上を有効成分として含有する活性酸素起因疾患予防剤。

【発明の詳細な説明】

【０００１】

【発明の属する技術分野】本発明は、体内における活性酸素の発生を抑制し、炎症、老化、発癌、心筋梗塞など活性酸素に起因して生じる様々な疾患を予防することができる薬剤に関する。

【０００２】

【従来の技術及び発明が解決しようとする課題】スーパーオキサイドアニオン（O_2^-）、ヒドロシキラジカル（・ＯＨ）、過酸化水素などの活性酸素は、生体内で多量に発生すると組織傷害を起こし、炎症、老化、発癌、心筋梗塞など様々な疾患を起こすといわれている。特に、ヒドロキシラジカルは活性酸素の中でも活性が高く、拡散律速的に生体にアタックして細胞膜等の脂質からＨを引き抜き、脂質を過酸化脂質ラジカルとして炎症や各種疾患を引き起こすと考えられている。

【０００３】これに対し、生体は各種活性酸素を低減するためのいくつかの酵素を備えている。例えば、スーパーオキサイドディスムターゼ（ＳＯＤ）は、スーパーオキサイドアニオンを不均化反応で過酸化水素に変換するが、カタラーゼやグルタチオンペルオキシダーゼは、過酸化水素を消去するとされている。しかしながら、ヒドロキシラジカルなど一部の活性酸素についてはこれらを低減する酵素は生体内に発見されておらず、また効力の面でも生体の酵素だけでは十分に活性酸素を低減できない場合がある。そこで、活性酸素に起因する様々な疾患を防ぐために、活性酸素を消失する物質、或いは活性酸素の発生を根本的に抑制する物質を生体に供給してやる必要がある。

【０００４】茶抽出成分については、従来、特開昭５９－１６６５８５号公報において、タンニン分画、特にエピカテキン、エピガロカテキン、エピカテキンガレート、エピガロカテキンガレートを有効成分した食品用および化粧品の抗酸化剤の発明が開示されているが、活性酸素の低減に関しては記載されていない。また、特開昭６４－２５７２６号公報には、茶から分離した縮合型タンニンを有効成分とする活性酸素フリーラジカル消去剤の発明が開示されているが、この発明は「消去」が意味するように、体内で発生した活性酸素が消去するというものであり、活性酸素の発生系に作用し発生そのものを抑制するという技術思想は記載されていなかった。

2

【０００５】今回本発明者らは、茶抽出成分が活性酸素の発生系に作用するメカニズムを究明すべく鋭意研究した結果、従来の考え方を覆すとも言える新たな発見をすることができ、この発見に基づいてなしたものである。

【０００６】

【課題を解決するための手段】すなわち、本発明者らの鋭意研究の結果、茶抽出成分は体内で発生した活性酸素を消去するのではなく、活性酸素の発生系に作用して活性酸素の発生そのものを抑制することを発見し、この発見に基づいて以下の本発明に到達したものである。

【０００７】本発明の第一は、茶の温水又は熱水抽出物、特に茶カテキンすなわち茶から抽出されるカテキン類を有効成分として含有する活性酸素発生抑制剤である。本発明における活性酸素とは、体内で発生する活性酸素すなわちスーパーオキサイドアニオン（O_2^-）、ヒドロシキラジカル（・ＯＨ）、過酸化水素などを意味している。

【０００８】本発明の第二は、茶の温水又は熱水抽出物、特に茶カテキンすなわち茶から抽出されるカテキン類を有効成分として含有する活性酸素起因疾患予防剤である。本発明における活性酸素起因疾患とは、活性酸素に起因する疾患、すなわち歯肉炎、歯周炎等の歯周病、肺炎、老化、イニシエーターやプロモーターに起因する肺癌及び胃癌、動脈硬化に起因する心筋梗塞等の循環器疾患、並びにベータアミロイドタンパクの毒性によるアルツハイマー型痴呆症などの疾患を意味している。

【０００９】上記本発明における茶とは、ツバキ科に由来する茶であり、茶カテキンとは、これらの茶に含有されているカテキン類、すなわちエピカテキンガレート、エピガロカテキンガレート、エピカテキン、エピガロカテキンのいずれか、或いはこれらの２種類以上を意味する。中でもエピカテキンガレート、エピガロカテキンガレートのいずれかが特に好ましいものと考えられる。

【００１０】茶の温水又は熱水抽出物としては、例えば、緑茶を熱水抽出処理し、この抽出物を乾燥させてカテキン濃度を約２２％とした緑茶エキス（伊藤園社製商品名：テアフラン３０）や、緑茶を熱水抽出処理し、この抽出物をカテキン以外の成分を排除するためにカラム法により処理し乾燥させて、カテキン濃度を約８５％とした緑茶エキス（伊藤園社製商品名：テアフラン９０Ｓ）は、茶カテキンを十分に含有し、かつ入手しやすいという点で好適な一例である。

【００１１】また、上記本発明において、茶の温水又は熱水抽出物乃至茶カテキンは、単独でも活性酸素発生抑制剤又は活性酸素起因疾患予防剤として有効であるが、ビタミンA（カロチノイド類）、ビタミンC、ビタミンE、グルタチオン、有機酸、アミノ酸などを配合すれば一層効果を高めることができる。特に医薬品又は医薬部外品として利用する場合には、ビタミンA（カロチノイド類）、ビタミンC、ビタミンE、グルタチオンを配合するのが好ましい。

【００１２】また、本発明の活性酸素発生抑制剤又は活性酸素起因疾患予防剤の剤型は、凍結乾燥或いは噴霧乾燥等により乾燥させて乾燥粉末として提供することも、また液剤、錠剤、散剤、顆粒、糖衣錠、カプセル、懸濁液、液剤、乳剤、アンプル、注射剤等として提供することもできる。

【００１３】また、本発明の活性酸素発生抑制剤及び活性酸素起因疾患予防剤は、医薬品、医薬部外品（化粧品、洗口剤などを含む）、健康食品、健康飲料などとして様々に提供することができる。例えば、医薬部外品として調製し、これを缶ドリンク飲料、瓶ドリンク飲料等の飲用形態、或いはタブレット、カプセル、顆粒等の形態として日常的に摂取しやすくすれば、日常的に摂取す＊ることにより生体に対して十分な薬理効果をもたらす医薬部外品として提供することができる。

【００１４】

【発明の実施の形態】

（Cu^{2+}/H_2O_2 反応系から発生するヒドロキシラジカルの低減能の測定）本実施例は、茶エキス（伊藤園社製テアフラン３０、伊藤園社製テアフラン９０S）及びヒドロキシラジカル消去剤として知られるDMSO（dimethyl sulfoxide）について、Cu^{2+}/H_2O_2 反応系から発生するヒドロキシラジカル低減能の測定をしたものであり、特にスピントラッピング剤であるDMPO（5,5-Dimethyl-1-pyrroline-N-oxide）の濃度を変化させ反応速度を変えることにより、反応速度論的な見地からヒドロキシラジカル低減能を検討したものである。

【００１５】（試料の調整）テアフラン３０は、緑茶を熱水抽出処理し、この抽出物を乾燥させた緑茶エキスであり、テアフラン９０Sは、緑茶を熱水抽出処理し、この抽出物をカテキン類以外の成分を排除するためにカラム法により処理し乾燥させた緑茶エキスである。両者のカテキン含有量（重量%）を以下に示す。

【００１６】

	テアフラン３０	テアフラン９０S
エピガロカテキン（EGC）・・・・・・・	１２．３０	２．００
エピガロカテキンガレート（EGCg）・・	６．８４	６６．２６
エピカテキン（EC）・・・・・・・・・・	１．６４	検出限界以下
エピカテキンガレート（ECg）・・・・・	１．０５	１５．２９

【００１７】また、DMSO（dimethyl sulfoxide）は、和光純薬工業社製のものを使用し、DMPO（5,5-Dimethyl-1-pyrroline-N-oxide）は、同仁化学研究所社より購入したものを使用した。以上の試料は、純水によって各種濃度に調製した。

【００１８】（測定方法）最終濃度１mMの$CuCl_2$ ５０μl、純水３０μl、９．２mM若しくは９２mMのDMPO２０μl、１００mMのH_2O_2 ５０μl、及び各試料５０μlをこの順序で混合（総量２００μl）して撹拌し、特殊偏平セルに吸引した。これより、Cu^{2+}/H_2O_2 反応系から発生するヒドロキシラジカルに各試料を反応させ、スピントラッピング剤のDMPOでトラップすれば、DMPO－OHアダクトとすることができる。測定は、ESR装置（日本電子社製ラジカルバイオセンサーFR８０）を用いて反応開始５０秒後に測定した。

【００１９】図1は、DMPO濃度を９．２mMとした場合におけるテアフラン３０、テアフラン９０S、及びDMSOの濃度とDMPO－OH収率との関係を示したグラフであり、図2は、DMPO濃度を９２mM又は９．２mMとした場合のテアフラン３０濃度とDMPO－OH収率との関係を示したグラフであり、図3は、DMPO濃度を９２mM又は９．２mMとした場合のテアフラン９０S濃度とDMPO－OH収率との関係を示し※たグラフである。

【００２０】（結果及び考察）図1の結果から、テアフラン３０及びテアフラン９０Sはいずれも、Cu^{2+}/H_2O_2 反応系から発生するヒドロキシラジカル（・OH）を低減することが確かめられ、その低減能力はテアフラン９０Sの方がテアフラン３０より大であった。一方、図2・図3の結果より、ESRスピントラッピング法のトラップ剤であるDMPOの濃度を変化させ反応速度を変えても、シグモイド曲線に変化はなかった。このことは、緑茶エキスであるテアフラン３０及びテアフラン９０Sはヒドロキシラジカル（・OH）を直接消去しているのではなく、Cu^{2+}/H_2O_2 反応系に作用し、結果としてヒドロキシラジカル（・OH）の発生そのものを抑制していることになる。したがって、テアフラン３０及びテアフラン９０S（緑茶抽出物）はいずれも、ヒドロキシラジカル発生抑制剤すなわち活性酸素発生抑制剤として有効であると共に、ヒドロキシラジカルの発生を抑制するのだから、活性酸素発生に起因する様々な疾患の予防剤としても有効であると考えられる。

【００２１】なお、上記測定においてCu^{2+}シグナルをESRで測定した際、EDTAを添加するとCu^{2+}シグナルはシフトしたが、テアフラン３０及びテアフラン９０S添加してもCu^{2+}シグナルはシフトせず、シグナル

5

量が減少したことが確認された。このことは、緑茶エキスであるテアフラン３０及びテアフラン９０Ｓは、Cu^{2+}をＥＤＴＡのようにキレート形成するのではなく、自身に配位結合させるか若しくは何らかの化学結合をさせるかしてCu^{2+}を変化させ、Cu^{2+}量を減少させたものと考えられる。

【００２２】次に、図2の結果より、テアフラン３０の場合、ＤＭＰＯ濃度９２ｍＭのＩＤ５０は7．９８ｍＭ、ＤＭＰＯ濃度９．２ｍＭのＩＤ５０は6．８６ｍＭであり、ＩＤ５０の平均値は7．４２ｍＭであった。図３の結果より、テアフラン９０Ｓの場合、ＤＭＰＯ濃度９２ｍＭのＩＤ５０は０．４４ｍＭ、ＤＭＰＯ濃度９．２ｍＭのＩＤ５０は０．５２ｍＭであり、ＩＤ５０の平均値は０．４８ｍＭであった。

【００２３】以上の結果より、テアフラン３０及びテアフラン９０Ｓの平均ＩＤ５０値を比較すると、テアフラン３０のＩＤ５０はテアフラン９０ＳのＩＤ５０に比べて１５．４６倍であった。この結果は、テアフラン９０Ｓの方がテアフラン３０に比べてCu^{2+}/H_2O_2 反応系におけるヒドロキシラジカル（・ＯＨ）の抑制率が高いことを示すばかりか、テアフラン３０及びテアフラン９０Ｓの成分比率を相関させて考えると、テアフラン３０のエピカテキンガレート（ＥＣｇ）濃度がテアフラン９０Ｓのほぼ１５倍である点から、Cu^{2+}/H_2O_2 反応系におけるヒドロキシラジカルの発生系にはＥＣｇが関与している可能性が高いと考えられる。ただし、図２及び図３のシグモイド曲線の引き方によってはテアフラン３０のＩＤ５０は約５ｍＭ程度となり、この結果、テアフラン３０＊

6

＊のＩＤ５０はテアフラン９０ＳのＩＤ５０の約１０倍となる。この結果を、テアフラン３０及びテアフラン９０Ｓの成分比率と相関させて考えてみると、テアフラン３０のエピガロカテキンガレート（ＥＧＣｇ）濃度がテアフラン９０Ｓのほぼ１０倍である点から、Cu^{2+}/H_2O_2 反応系におけるヒドロキシラジカルの発生系にはＥＧＣｇが関与している可能性があるとも考えられる。

【００２４】（実施例１）テアフラン３０を６ｍＭ以上、テアフラン９０Ｓを０．６ｍＭ以上の濃度となるように以下の配合割合で、活性酸素発生抑制効果及び活性酸素発生起因疾患予防効果のある化粧品、又は医薬部外品の範疇に含まれる洗口剤を作成した。なお、上記テアフラン３０の６ｍＭ、及びテアフラン９０Ｓの０．６ｍＭの数値は、図１において、それぞれシグモイド曲線を引いた場合のＩＤ５０に対応する濃度に基づいた値である。

緑茶エキス・・・・・・・・・	１．０　重量％
パラオキシ安息香酸エステル・	０．０５重量％
プロピレングリコール・・・・	１．０　重量％
濃グリセリン・・・・・・・・	１．０　重量％
クエン酸ナトリウム・・・・・	０．０５重量％
香料・・・・・・・・・・・・	適量
精製水・・・・・・・・・・・	９５．０　重量％

【００２５】（実施例２）緑茶エキス（テアフラン３０又はテアフラン９０Ｓ）を以下の割合で配合し、ヒドロキシラジカルの発生を抑制することによって脂質過酸化などの老化を予防する効果のある食品、又は医薬品を作成した。

茶カテキン・・・・・・・・・	７０．０ｍｇ
ビタミンＣ・・・・・・・・・	５０．０ｍｇ
乳化オリゴ糖・・・・・・・・	９０．０ｍｇ
造粒剤・・・・・・・・・・・	６０．０ｍｇ
結晶セルロース・・・・・・・	８０．０ｍｇ
還元麦芽糖水飴・・・・・・・	９０．０ｍｇ
シュークロース・・・・・・・	６０．０ｍｇ
香料・・・・・・・・・・・・	適量
（合計）・・	５００．０ｍｇ

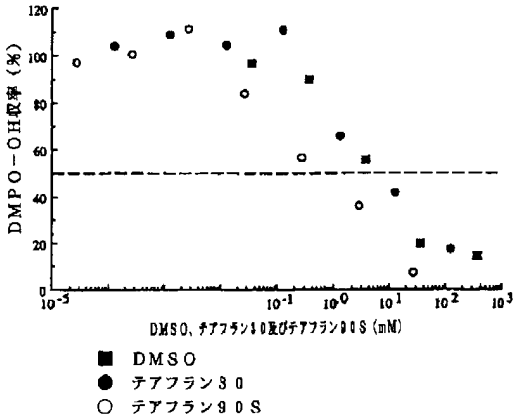
【図面の簡単な説明】

【図１】ＤＭＰＯ濃度を９．２ｍＭとした場合におけるテアフラン３０、テアフラン９０Ｓ及びＤＭＳＯの濃度とＤＭＰＯ－ＯＨ収率との関係を示したグラフである。

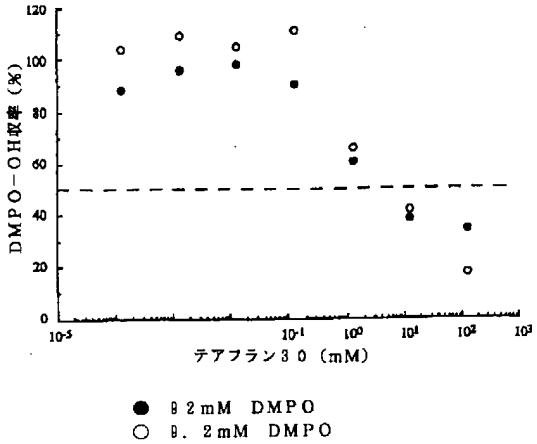
【図２】ＤＭＰＯ濃度を９２ｍＭ又は９．２ｍＭとした※場合のテアフラン３０濃度とＤＭＰＯ－ＯＨ収率との関係を示したグラフである。

【図３】ＤＭＰＯ濃度を９２ｍＭ又は９．２ｍＭとした場合のテアフラン９０Ｓ濃度とＤＭＰＯ－ＯＨ収率との関係を示したグラフである。

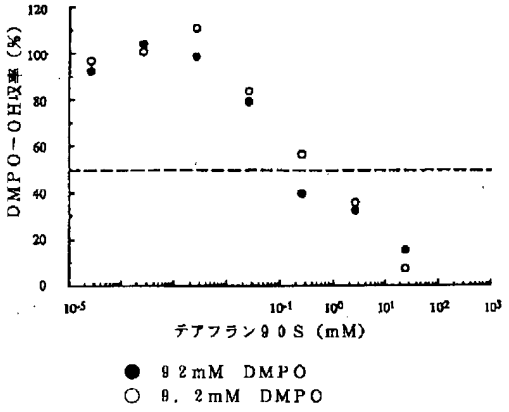
【図1】



【図2】



【図3】



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